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Effects of Curcumin Supplementation on Blood Glucose, Insulin Resistance and Androgens in Patients with Polycystic Ovary Syndrome:

A Randomized Double-Blind Placebo-Controlled Clinical Trial

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Conflicts of Interest

The authors have no conflicts of interest to declare.

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Abstract

Background: Curcumin is a biologically active phytochemical ingredient found in turmeric. It has several pharmacologic effects that might benefit patients with polycystic ovary syndrome (PCOS).

Objective: We hypothesized curcumin to be effective in improving blood sugar levels, insulin resistance and hyperandrogenism in individuals with PCOS.

Methods: In a randomized double-blind placebo-controlled trial, individuals with PCOS were treated with curcumin (500 mg thrice daily) or placebo for 12 weeks. Primary outcome measures were fasting plasma glucose (FPG), fasting insulin (FI), sex hormone levels, and hirsutism (Ferriman-Gallwey [mFG] questionnaire). Secondary outcomes included anthropometric measurements.

Results: Of 72 randomized individuals, 67 completed the trial. The two groups were comparable at baseline. At the end of the study, FPG and Dehydroepiandrosterone levels had decreased significantly in the intervention group compared to control (difference of change (post-pre) between intervention and placebo groups: -4.11mg/dL; 95% CI: -8.35, -0.35 mg/dL; p = 0.033 and -26.53 microg/dL; 95% CI: -47.99, -4.34 µg/dL; p = 0.035, respectively). We also observed a statistically non-significant increase (p= 0.082) in Estradiol levels in the intervention group compared to control. No serious adverse events were reported throughout the trial.

Conclusions: Curcumin might be a safe and useful supplement to ameliorate PCOS-associated hyperandrogenemia and hyperglycemia. However, longer trials investigating different dosages in longer durations are needed to underpin these findings.

Keywords: curcumin; polycystic ovary syndrome; glucose; insulin; androgens

Abbreviations

AMPK: AMP-activated protein kinase

BMI: body mass index

DHEAS: Dehydroepiandrosterone

FI: fasting insulin

FPG: fasting plasma glucose

FSH: Follicle-Stimulating Hormone

GLP-1: Glucagon-like peptide-1

GLUT4: Glucose transporter type 4

HO-1: Heme oxygenase-1

HOMA-IR: Homeostatic model assessment

IGT: impaired glucose tolerance

IL-6: Interleukin 6

IPAQ: international physical activity questionnaire

LH: Luteinizing Hormone

MAPK: mitogen-activated protein kinase

mFG: modified Ferriman-Gallwey

NSAIDs: Non-steroidal anti-inflammatory drugs

Nrf2: Nuclear factor E2-related factor 2

PI3K/ AKT: Phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)

PCOS: Polycystic ovary syndrome

PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha

QUICKI: quantitative insulin sensitivity check index

SIRT1: Sirtuin 1

TNF-α: Tumor necrosis factor alpha

WC: waist circumference

Introduction

Polycystic ovary syndrome (PCOS) is the most prevalent endocrine disorder and the leading cause of infertility among women in the reproductive age, affecting approximately 15% of these(Teede et al., 2013). Various factors have been found to contribute to the disease onset, but the etiology is mostly unknown and partly attributed to genetics(Legro et al., 2013). PCOS is characterized by polycystic ovarian morphology, androgen excess, insulin resistance and chronic oligo-anovulation (Priyanka et al., 2018; Teede et al., 2018). A large number of patients with PCOS have insulin resistance and hyperinsulinemia, which suggests that insulin may have a critical role in the pathophysiology or maintenance of PCOS(Dahan et al., 2019). In addition, excessive androgens in PCOS patients cause changes in body fat distribution and hirsutism(Anagnostis et al., 2018). Regarding the relationship between obesity and PCOS, it seems as if nutrition may play a significant role in the incidence and control of the disease(Agrawal et al., 1998; Chin, 2016). Nutritional interventions have been found to be successful in women with PCOS(Sadeghi et al., 2017). Dietary factors including antioxidant ingredients may improve metabolic disorders associated with PCOS(Borzoei et al., 2018). Among the antioxidant factors, curcumin has recently received much attention(Sahebkar et al., 2015).

Curcumin is a yellow polyphenolic pigment, low-insoluble in water; a mixture of curcuminoid derived from turmeric (Curcuma longa)(Julie et al., 2009). Curcumin has anti-oxidant and anti-inflammatory properties through several mechanisms such as effects on gene expression and cellular signaling(Kunnumakkara et al., 2017). It has been proven that curcumin ameliorates insulin resistance by increasing oxidation of fatty acid and glucose in peripheral tissues(Dehghani et al., 2020; Na et al., 2011). Curcumin has beneficial impacts on PCOS in pre-clinical animal models. Its impact was comparable to that of Clomiphene citrate, one of the major treatment

options for ovulation induction in PCOS patients(Reddy et al., 2016). However, no randomized clinical trial has been performed in humans to evaluate the effect of curcumin supplementation on glycemic and hormonal parameters in PCOS patients. Accordingly, in this randomized double-blind placebo-controlled clinical trial, we investigated the effects of curcumin on glycemic control and hormonal parameters in PCOS patients.

Methods and Design

Study Design

This study was conducted at the Arash Women's Hospital, Tehran University of Medical Sciences, Tehran, Iran. Women with polycystic ovary were diagnosed by using the Rotterdam diagnostic criteria,(Rotterdam et al., 2004) which are (two of three need to be fulfilled): a) oligoovulation (period cycle greater than 35 days), b) hyperandrogenism (clinical or laboratory) with clinical signs of hirsutism, acne and hair loss with a male pattern and increased testosterone levels or Dehydroepiandrosterone (DHEAS) and c) PCOS-suggestive morphological findings in ovarian ultrasonography.

Inclusion and Exclusion Criteria

For the present study, PCOS women aged 18–49 years (considered to be in a reproductive age) were included. They had to voluntarily participate in the study, have a definitive diagnosis of PCOS for at least 2 years (made by a specialist physician in the mild to moderate phase) with impaired glucose tolerance (IGT), be a consumer of only one of the metformin or clomiphene drug groups, have a body mass index (BMI) higher than 25 and less than 30 kg/m^2. Patients were excluded if: a) Occurrence of other hormonal diseases/disorders, autoimmune diseases, cancer,

inflammatory disease, infections, pregnancy or lactation, b) use of multi-vitamin-mineral, omega-3, polyphenolic and antioxidant supplements, as well as the use of anticoagulants such as heparin and warfarin or aspirin, blood cholesterol lowering drugs (statins), Non-steroidal anti-inflammatory drugs (NSAIDs), such as Ibuprofen, Aspirin and Diclofenac, antihistamines, calcium channel antagonists, anti-TNF drugs, glucocorticoids (cortisone, prednisolone) or spironolactone during the past month.

Intervention

Curcumin and placebo (maltodextrin) capsules were prepared by KAREN Pharma in Yazd, Iran. Each capsule contained 500 mg of curcumin powder or maltodextrin. Shape, size, smell and color of placebo capsules were completely similar to the curcumin capsules. Curcumin and placebo capsules were provided to both groups monthly for 12 weeks. Participants took 3 capsules daily (1500 mg overall per day). The capsule packages were checked at the end of each month and the number of remaining treatment and placebo capsules were counted. Patients were asked to keep their normal lifestyle constant, including the physical activity level and their PCOS diet. To ascertain participant retention and evaluate the participants' compliance during the trial, one researcher contacted them every 15 days by telephone to see whether participants consumed the capsules and to investigate whether they experienced any side effects during the study period.

Study Outcomes

Primary outcomes of this trial were changes in fasting plasma glucose (FPG), fasting insulin (FI), sex hormones (Estradiol, Dehydroepiandrosterone (DHEA), Follicle-Stimulating Hormone (FSH) and Luteinizing Hormone (LH)), and modified Ferriman-Gallwey (mFG) questionnaire for

hirsutism. Secondary outcomes of this study were changes in waist circumference (WC), weight and body-mass index (BMI).

Procedure

Informed consent was obtained from all patients. Patients in both groups visited the hospital twice: at baseline and after 12 weeks of intervention. Socio-demographic information were obtained by a face-to-face interview. At each visit, anthropometric parameters (height, weight and WC) were measured, for the evaluation of biochemical parameters, 10 ml blood sample were collected in rested position and after 8-10 hours of fasting. Primary blood sampling was performed on the third day of the menopausal cycle of women, and in women without menstrual periods, these blood samples were taken at the earliest opportunity after recruitment. The short form of international physical activity questionnaire (IPAQ) and 24-h food recall were obtained from all subjects.

Anthropometric parameters such as height, weight and waist and hip circumferences were measured at baseline and the end of the trial in standard conditions. Height and weight were measured by a Seca scale with a stadiometer. Weight was measured with the participants wearing lightest clothes and without shoes. Height was recorded in a straight standing position (without shoes). BMI was calculated by dividing weight (kg) by height m^2.

Measurement of Biochemical Parameters

A blood sample of 10 ml was collected from each participant after 8-10 hours overnight fasting at baseline and at the end of 12 weeks. Serum samples for FPG, FI, FSH, LH, DHEA and estradiol assays were frozen and stored at −80°C until analyzed. Serum concentrations of FPG, FI, FSH, LH and DHEA were determined by using enzymatic photometric methods (Pars Azmun kits; Pars

Azmun, Tehran, Iran). Homeostatic model assessment (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) were obtained through calculation based on FPG and FSI levels. HOMA-IR was calculated according to the formula: FI (microU/L) x FPG (nmol/L)/22.5 and QUICKI was derived calculating the inverse of the sum of logarithms of FI and FPG: 1 / (log (FI μU/mL) + log (FPG mg/dL)).

Randomization

Block randomization was conducted using Stata statistical software, version 13. Six blocks were chosen. Treatment and placebo were similarly provided, prepared in the same color and the same smell, and coded according to the random allocation. None of the patients were aware of the prescribed treatment until end of study.

Sample Size

Based on our clinical expectation, we considered that a difference of 22 mg/dL in FPG between the two randomized groups as a clinically important difference. Based on $\alpha = 0.05$ and power $\beta = 0.80$, $n = 30$ per study arm was estimated to be an adequate sample size. To account for an expected drop-out rate of 20%, we included 36 patients in each group.

Statistical Analysis

Data were analyzed according to intention-to-treat analysis. Baseline characteristics were compared between the two groups by using an independent sample t-test for continuous data and a chi-square test for categorical data. The changes in primary and secondary outcomes of the patients between the beginning and end of the intervention in each group were compared by paired

sample t-tests. Also, changes in primary and secondary outcomes of the patients between the two intervention groups were compared by independent sample t-tests. The magnitude of effect is presented as the mean difference and its 95% confidence interval. A multiple linear regression was used to adjust for the effects of baseline values (dependent variable) such as BMI and age on primary outcomes. The study statistician was blinded concerning which group received which treatment.

Ethical Considerations

Approval by the Ethics Committee of Iran University of Medical Sciences. We obtained informed consent from all patients. This randomized clinical trial has been approved in Iranian Registry of Clinical Trials at 2019-01-23 (registration reference IRCT20091114002709N50).

Results

72 patients with PCOS were randomly assigned to the intervention group (n = 36) and the placebo group (n = 36) (**Figure 1**). Two patients in the curcumin group (n = 1 pregnant, n = 1 lost to follow-up) and three patients in the placebo group (n = 1 emigration, n = 1 getting pregnant, n = 1 personal reasons) withdrew from study. Eventually, 67 patients, including 34 patients in the intervention and 33 patients in the placebo group, completed the study. There were no serious or mild adverse events reported or observed in any group. The sampling of the study began on October 1, 2018 and continued by the end of May 2019. Follow-up was completed by the end of October 2019.

Table 1 shows that there were no significant differences between the two groups in sociodemographic features. This indicates a comparable starting point between the two randomly assigned groups.

Total energy, macronutrients and antioxidant intake of diet at baseline and at the end of the study are indicated in **Table 2**. No significant differences in energy intake and other dietary parameters were detected between the groups at baseline, and energy and nutrient intake did not change significantly in any of the groups during the trial. Additionally, there was no significant difference in the physical activity levels of patients between two groups during the 12 weeks.

Biochemical and hormonal parameters are presented in **Table 3**. No significant differences were detected between the groups at baseline regarding FPG, FI, HOMA-IR, QUICKI, FSH, LH, DHEA, Estradiol, mFG, BMI and WC.

At the end of the study, mean FPG levels had decreased in the intervention group and were significantly lower in the intervention group compared to the placebo group (difference between intervention and placebo groups: -4.11 mg/dL; p (adjusted) = 0.048). Similar results were obtained concerning Dehydroepiandrosterone levels (difference: -26.53 microg/dL; p (adjusted) = 0.035). Estradiol levels had increased in the intervention group and decreased in the control group (difference: 4.38 picog/dL; p(adjusted) = 0.082), but this difference was not statistically significant. Insulin parameters and other hormonal parameters such as LH, FSH, FI, HOMA-IR, QUICKI, BMI and WC were all not significantly different between the study groups at the end of the trial.

Discussion

Curcumin is an active pigment of turmeric and has a polyphenolic structure(Cicero et al., 2016). In the present randomized placebo-controlled double-blind trial, intake of 1,500-mg curcumin supplement per day for 12 weeks in patients with PCOS significantly reduced serum FPG and

DHEA. However, we did not find a statistically significant effect on BMI, FI, HOMA-IR, QUICKI, mFG, LH or FSH. While changes in estradiol were not statistically significant, levels increased in the intervention group but decreased in the placebo group, indicating a potential beneficial effect. To the best of our knowledge, this is the first trial investigating the impact of curcumin supplementation on glycemic and hormonal parameters in PCOS patients. Recently, two studies evaluated the effect of curcumin on gene expression of oxidative stress parameters(Heshmati et al., 2020) and glycemic and lipid profile parameters in PCOS patients(Jamilian et al., 2020). Jamilian et al. showed that curcumin intake significantly decreased FBS, Insulin, Insulin resistance, total cholesterol, and LDL-cholestrol. Also, curcumin intake was associated with a significant increase in HDL-cholesterol and Insulin sensitivity(Jamilian et al., 2020). The results of the work by Heshmati et al. indicated that curcumin intake might decrease oxidative stress in PCOS patients via affecting mRNA gene expression of Silent information regulator 1 (SIRT1) and Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α)(Heshmati et al., 2020). Previous animal studies had indicated that curcumin supplementation exerts its protective impact by improving all PCOS-related parameters(Reddy et al., 2016).

Studies regarding the impact of curcumin supplementation on type 2 diabetes mellitus have demonstrated that curcumin significantly decreases plasma FPG concentrations(Asadi et al., 2019; Chuengsamarn et al., 2014). Curcumin supplementation also improved insulin resistance – Similar to the decrease in insulin resistance in our study, however, the trend in our study was not statistically significant. However, Wickenberg et al. investigated the effects of curcumin on healthy individuals and showed that it did not alter insulin and glucose levels(Wickenberg et al., 2010). The difference between the results of Wickenberg et al. and our study may be due to both

the short-term use of curcumin in their study and the differences in the health status of participants. Curcumin supplements appear to be more effective in people who are ill or affected by oxidative stress caused by the respective disease(Pari et al., 2008). Other studies indicated that postprandial glucose levels were significantly lower in healthy subjects with curcumin supplementation intake(Thota et al., 2018).

Several mechanisms have been suggested for the effect of curcumin in reducing blood glucose. In a pre-clinical study, curcumin showed an additive inhibitory impact with insulin on both hepatic glycogenolysis and gluconeogenesis, indicating that curcumin might inhibit hepatic glucose production (Cicero et al., 2020; Fujiwara et al., 2008). In addition, it has been shown that curcumin increased glucose uptake through activating AMP-activated protein kinase (AMPK) by increasing its phosphorylation. Besides, curcumin increased the function of mitogen-activated protein kinase kinase (MEK)3/6-p38 and mitogen-activated protein kinase (MAPK) signaling pathways downstream of the AMPK cascade, thereby increasing cellular glucose intake (Akbari et al., 2020; Kim et al., 2010). Investigators also suggested that co-treatment of curcumin with insulin leads to a mutual synergistic activation of both AMPK/ACC and PI3-kinase/Akt pathways(Kang et al., 2010; Namazi et al., 2018). Curcumin seems to affect the glucose metabolism by changes in glucose-related enzymal activity: Curcumin increases hepatic glucokinase activity, whereas glucose-6-phosphatase and phosphoenolpyruvate carboxykinase activities were significantly decreased by curcumin supplementation(Seo et al., 2008). Adding to this, previous investigations indicated that curcumin stimulates secretion of Glucagon-like peptide-1 (GLP-1) (Kato et al., 2017). Concerning effects of curcumin on insulin resistance through increased glucose uptake by glucose transporters like Glucose transporter type 4 (GLUT4), no definitive conclusions have been reached yet(Green et al., 2014). Antioxidant effects of curcumin could be another possible reason

to improve glucose intolerance; short-term intake of curcumin in high fat diet mice improved glucose intolerance through decreasing muscular oxidative stress by activating Nuclear factor E2-related factor 2 (Nrf2) function(He et al., 2012).

The results of our study indicate that curcumin significantly reduces the amount of DHEA and might even increase estradiol levels in women with PCOS. To date, there is no similar study about the effects of curcumin supplementation on sex hormones in women with PCOS. However, studies of the effect of curcumin and its analogues on androgen receptors have reported that curcumin supplementation inhibits or even destroys the above-mentioned receptors(Choi et al., 2010; Shi et al., 2009). Curcumin significantly downregulated the expression of Ovarian androgen receptor proteins and simultaneously decreased Cyclooxygenase-2 protein(Tiwari-Pandey et al., 2009). Other studies have shown that curcumin increases the expression of SIRT1 (Heshmati et al., 2020; Yang et al., 2013). SIRT1 is a genetic factor leading to a decline in androgen receptor function(Fu et al., 2006).

Ovarian dysfunction and damage are one of the main features of patients with PCOS(Rosenfield et al., 2016). It has been shown that curcumin effectively reduces apoptosis, oxidative stress and ovarian injury via a mechanism involving the Nrf2/ Heme oxygenase-1 (HO-1) and Phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathways. Curcumin improves ovarial function by reducing FSH and LH levels(Yan et al., 2018). In addition, inflammation and inflammatory factors play a central role in the pathogenesis of PCOS(Ganie et al., 2019). Potent anti-inflammatory properties of curcumin in lowering circulating Tumor necrosis factor alpha (TNF-α) (Sahebkar et al., 2016) and Interleukin 6 (IL-6) (Derosa et al., 2016) concentrations have been found two in systematic reviews with meta-analyses. In addition, it has been shown that curcumin intake significantly increases PGC-1α gene expression, which is has

been connected to reduced oxidative stress levels and an increase in antioxidant enzyme activity such as Gpx. (Heshmati et al., 2020). Therefore, curcumin may improve hormonal profiles in patients with PCOS by reducing inflammation and oxidative stress and improving ovarian function. Although our study did not find any significant effects of curcumin on LH and FSH hormones, results might differ in other doses and treatment durations.

There are several limitations to our study. Firstly, it has been shown that nano-curcumin is an even more efficient antioxidant and anti-inflammatory preparation of curcumin. If we had used nano curcumin, we could possibly have detected an even greater effect of curcumin in clinical parameters relevant to PCOS patients. Secondly, we did not evaluate some antioxidant factors such as chromium. Finally, we also did not evaluate factors which might have an important clinical value for PCOS patients, such as inflammatory markers, lipid profile parameters and Anti-Müllerian hormone levels.

In conclusion, our randomized placebo-controlled double-blind trial shows that curcumin supplementation for three months reduces FPG and DHEA in patients with PCOS. While it seems that curcumin might also elevate estradiol levels, we found no changes in other glycemic or hormonal parameters. Accordingly, curcumin supplementation may be a beneficial and safe supplement in patients suffering from PCOS. Trials of longer duration that investigate different dosages are needed to underpin these findings.

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Authors' Contributions: J.H and M.S. contributed to the study design, data analysis, and interpretation; and drafted and edited the manuscript. F.SH. and A.M contributed to the statistical analysis and edited the manuscript. M.M contributed to the data collection and edited the

manuscript. M.F.M and M.S. are contributed to performing search and data collection. A.P interpreted the data, edited the manuscript, and prepared the final version of the article.

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Notes

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Conflict of interests

The authors have no conflict of interest to declare

References

Agrawal, R., Sladkevicius, P., Engmann, L., Conway, G., Payne, N., Bekis, J., . . . Jacobs, H. (1998). Serum vascular endothelial growth factor concentrations and ovarian stromal blood flow are increased in women with polycystic ovaries. *Human reproduction, 13*(3), 651-655.

Akbari, A., Mobini, G. R., Agah, S., Morvaridzadeh, M., Omidi, A., Potter, E., . . . Dehghani, S. (2020). Coenzyme Q10 supplementation and oxidative stress parameters: a systematic review and meta-analysis of clinical trials. *European Journal of Clinical Pharmacology*, 1-17.

Anagnostis, P., Tarlatzis, B. C., & Kauffman, R. P. (2018). Polycystic ovarian syndrome (PCOS): Long-term metabolic consequences. *Metabolism, 86*, 33-43.

Asadi, S., Gholami, M. S., Siassi, F., Qorbani, M., Khamoshian, K., & Sotoudeh, G. (2019). Nano curcumin supplementation reduced the severity of diabetic sensorimotor polyneuropathy in patients with type 2 diabetes mellitus: A randomized double-blind placebo-controlled clinical trial. *Complementary therapies in medicine, 43*, 253-260.

Borzoei, A., Rafraf, M., Niromanesh, S., Farzadi, L., Narimani, F., & Doostan, F. (2018). Effects of cinnamon supplementation on antioxidant status and serum lipids in women with polycystic ovary syndrome. *Journal of traditional and complementary medicine, 8*(1), 128-133.

Chin, K.-Y. (2016). The spice for joint inflammation: anti-inflammatory role of curcumin in treating osteoarthritis. *Drug Design, Development and Therapy, 10*, 3029.

Choi, H., Lim, J., & Hong, J. (2010). Curcumin interrupts the interaction between the androgen receptor and Wnt/β-catenin signaling pathway in LNCaP prostate cancer cells. *Prostate cancer and prostatic diseases, 13*(4), 343.

Chuengsamarn, S., Rattanamongkolgul, S., Phonrat, B., Tungtrongchitr, R., & Jirawatnotai, S. (2014). Reduction of atherogenic risk in patients with type 2 diabetes by curcuminoid extract: a randomized controlled trial. *The Journal of nutritional biochemistry, 25*(2), 144-150.

Cicero, A. F., & Colletti, A. (2016). Role of phytochemicals in the management of metabolic syndrome. *Phytomedicine, 23*(11), 1134-1144.

Cicero, A. F., Sahebkar, A., Fogacci, F., Bove, M., Giovannini, M., & Borghi, C. (2020). Effects of phytosomal curcumin on anthropometric parameters, insulin resistance, cortisolemia and non-alcoholic fatty liver disease indices: a double-blind, placebo-controlled clinical trial. *European Journal of Nutrition, 59*(2), 477-483.

Dahan, M. H., & Reaven, G. (2019). Relationship among obesity, insulin resistance, and hyperinsulinemia in the polycystic ovary syndrome. *Endocrine*, 1-5.

Dehghani, S., Hosseini, M., Haghgoo, S., Changizi, V., Akbari Javar, H., Khoobi, M., & Riahi Alam, N. (2020). Multifunctional MIL-Cur@ FC as a theranostic agent for magnetic resonance imaging and targeting drug delivery: in vitro and in vivo study. *Journal of Drug Targeting*, 1-13.

Derosa, G., Maffioli, P., Simental-Mendia, L. E., Bo, S., & Sahebkar, A. (2016). Effect of curcumin on circulating interleukin-6 concentrations: a systematic review and meta-analysis of randomized controlled trials. *Pharmacological research, 111*, 394-404.

Fu, M., Liu, M., Sauve, A. A., Jiao, X., Zhang, X., Wu, X., . . . Avantaggiati, M. L. (2006). Hormonal control of androgen receptor function through SIRT1. *Molecular and cellular biology, 26*(21), 8122-8135.

Fujiwara, H., Hosokawa, M., Zhou, X., Fujimoto, S., Fukuda, K., Toyoda, K., . . . Inagaki, N. (2008). Curcumin inhibits glucose production in isolated mice hepatocytes. *Diabetes Res Clin Pract, 80*(2), 185-191. doi: https://doi.org/10.1016/j.diabres.2007.12.004

Ganie, M. A., Sahar, T., Rashid, A., Wani, I., Nisar, S., Sathyapalan, T., . . . Geer, I. (2019). Comparative evaluation of biomarkers of inflammation among Indian women with Polycystic Ovary Syndrome (PCOS) consuming vegetarian versus non-vegetarian diet. *Frontiers in Endocrinology, 10*, 699.

Green, A., Krause, J., & Rumberger, J. M. (2014). Curcumin is a direct inhibitor of glucose transport in adipocytes. *Phytomedicine, 21*(2), 118-122.

He, H.-J., Wang, G.-Y., Gao, Y., Ling, W.-H., Yu, Z.-W., & Jin, T.-R. (2012). Curcumin attenuates Nrf2 signaling defect, oxidative stress in muscle and glucose intolerance in high fat diet-fed mice. *World Journal of Diabetes, 3*(5), 94.

Heshmati, J., Golab, F., Morvaridzadeh, M., Potter, E., Akbari-Fakhrabadi, M., Farsi, F., . . . Shidfar, F. (2020). The effects of curcumin supplementation on oxidative stress, Sirtuin-1 and peroxisome proliferator activated receptor γ coactivator 1α gene expression in polycystic ovarian syndrome (PCOS) patients: A randomized placebo-controlled clinical trial. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 14*(2), 77-82.

Jamilian, M., Foroozanfard, F., Kavossian, E., Aghadavod, E., Shafabakhsh, R., Hoseini, A., & Asemi, Z. (2020). Effects of curcumin on body weight, glycemic control and serum lipids in women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial. *Clinical Nutrition ESPEN*.

Julie, S., & Jurenka, M. (2009). Anti-inflammatory properties of curcumin, a major constituent. *Alternative medicine review, 14*(2).

Kang, C., & Kim, E. (2010). Synergistic effect of curcumin and insulin on muscle cell glucose metabolism. *Food and Chemical Toxicology, 48*(8-9), 2366-2373.

Kato, M., Nishikawa, S., Ikehata, A., Dochi, K., Tani, T., Takahashi, T., . . . Tsuda, T. (2017). Curcumin improves glucose tolerance via stimulation of glucagon-like peptide-1 secretion. *Molecular nutrition & food research, 61*(3), 1600471.

Kim, J. H., Park, J. M., Kim, E. K., Lee, J. O., Lee, S. K., Jung, J. H., . . . Kim, H. S. (2010). Curcumin stimulates glucose uptake through AMPK-p38 MAPK pathways in L6 myotube cells. *Journal of cellular physiology, 223*(3), 771-778.

Kunnumakkara, A. B., Bordoloi, D., Padmavathi, G., Monisha, J., Roy, N. K., Prasad, S., & Aggarwal, B. B. (2017). Curcumin, the golden nutraceutical: multitargeting for multiple chronic diseases. *British Journal of Pharmacology, 174*(11), 1325-1348.

Legro, R. S., Arslanian, S. A., Ehrmann, D. A., Hoeger, K. M., Murad, M. H., Pasquali, R., & Welt, C. K. (2013). Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. *The Journal of Clinical Endocrinology & Metabolism, 98*(12), 4565-4592.

Na, L.-X., Zhang, Y.-L., Li, Y., Liu, L.-Y., Li, R., Kong, T., & Sun, C.-H. (2011). Curcumin improves insulin resistance in skeletal muscle of rats. *Nutrition, Metabolism and Cardiovascular Diseases, 21*(7), 526-533.

Namazi, N., Larijani, B., Ayati, M. H., & Abdollahi, M. (2018). The effects of Nigella sativa L. on obesity: A systematic review and meta-analysis. *Journal of ethnopharmacology, 219*, 173-181.

Pari, L., Tewas, D., & Eckel, J. (2008). Role of curcumin in health and disease. *Archives of physiology and biochemistry, 114*(2), 127-149.

Priyanka, R. H., Hemanth, K., Apurva, M., Bakshi, V., & Kumar, B. H. (2018). Observational study on risk factors, complications and management of polycystic ovarian syndrome.

Reddy, P. S., Begum, N., Mutha, S., & Bakshi, V. (2016). Beneficial effect of Curcumin in Letrozole induced polycystic ovary syndrome. *Asian Pacific Journal of Reproduction, 5*(2), 116-122.

Rosenfield, R. L., & Ehrmann, D. A. (2016). The pathogenesis of polycystic ovary syndrome (PCOS): the hypothesis of PCOS as functional ovarian hyperandrogenism revisited. *Endocrine reviews, 37*(5), 467-520.

Rotterdam, E., & Group, A.-S. P. C. W. (2004). Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Human Reproduction (Oxford, England), 19*(1), 41.

Sadeghi, A., Djafarian, K., Mohammadi, H., & Shab-Bidar, S. (2017). Effect of omega-3 fatty acids supplementation on insulin resistance in women with polycystic ovary syndrome: Meta-analysis of randomized controlled trials. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 11*(2), 157-162.

Sahebkar, A., Cicero, A. F., Simental-Mendia, L. E., Aggarwal, B. B., & Gupta, S. C. (2016). Curcumin downregulates human tumor necrosis factor-α levels: A systematic review and meta-analysis ofrandomized controlled trials. *Pharmacological research, 107*, 234-242.

Sahebkar, A., Serban, M.-C., Ursoniu, S., & Banach, M. (2015). Effect of curcuminoids on oxidative stress: A systematic review and meta-analysis of randomized controlled trials. *Journal of functional foods, 18*, 898-909.

Seo, K. I., Choi, M. S., Jung, U. J., Kim, H. J., Yeo, J., Jeon, S. M., & Lee, M. K. (2008). Effect of curcumin supplementation on blood glucose, plasma insulin, and glucose homeostasis related enzyme activities in diabetic db/db mice. *Molecular nutrition & food research, 52*(9), 995-1004.

Shi, Q., Shih, C.-Y., & Lee, K. (2009). Novel anti-prostate cancer curcumin analogues that enhance androgen receptor degradation activity. *Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents), 9*(8), 904-912.

Teede, H. J., Joham, A. E., Paul, E., Moran, L. J., Loxton, D., Jolley, D., & Lombard, C. (2013). Longitudinal weight gain in women identified with polycystic ovary syndrome: results of an observational study in young women. *Obesity, 21*(8), 1526-1532.

Teede, H. J., Misso, M. L., Costello, M. F., Dokras, A., Laven, J., Moran, L., . . . Norman, R. J. (2018). Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Human Reproduction, 33*(9), 1602-1618.

Thota, R. N., Dias, C. B., Abbott, K. A., Acharya, S. H., & Garg, M. L. (2018). Curcumin alleviates postprandial glycaemic response in healthy subjects: a cross-over, randomized controlled study. *Scientific reports, 8*(1), 13679.

Tiwari-Pandey, R., & Ram Sairam, M. (2009). Modulation of ovarian structure and abdominal obesity in curcumin-and flutamide-treated aging FSH-R haploinsufficient mice. *Reproductive Sciences, 16*(6), 539-550.

Wickenberg, J., Ingemansson, S. L., & Hlebowicz, J. (2010). Effects of Curcuma longa (turmeric) on postprandial plasma glucose and insulin in healthy subjects. *Nutrition journal, 9*(1), 43.

Yan, Z., Dai, Y., Fu, H., Zheng, Y., Bao, D., Yin, Y., . . . Hou, D. (2018). Curcumin exerts a protective effect against premature ovarian failure in mice. *Journal of molecular endocrinology, 60*(3), 261-271.

Yang, Y., Duan, W., Lin, Y., Yi, W., Liang, Z., Yan, J., . . . Li, Y. (2013). SIRT1 activation by curcumin pretreatment attenuates mitochondrial oxidative damage induced by myocardial ischemia reperfusion injury. *Free Radical Biology and Medicine, 65*, 667-679.

Table 1. Baseline characteristic after random assignment

		Total	Groups		P
			Intervention(A)(n=34)	Control(B)(n=33)	
Age	Mean ± SD	30.86 ± 6.66	30.97 ± 5.20	30.75 ± 7.97	0.897†
	Median (range)	30 (18 to 52)	31 (18 to 41)	29 (20 to 52)	
Marriage	Single	7 (10.4%)	3 (8.8%)	4 (12.1%)	0.906*
	Married	58 (86.6%)	30 (88.2%)	28 (84.8%)	
	Divorced	2 (3.0%)	1 (2.9%)	1 (3.0%)	
Smoking	Yes	3 (4.5%)	1 (2.9%)	2 (6.1%)	0.537*
	No	64 (95.5%)	33 (97.1%)	31 (53.3%)	
Occupation	Employed	19 (28.4%)	12 (35.3%)	7 (21.2%)	0.201*
	Housewife	48 (71.6%)	22 (64.7%)	26 (78.8%)	
Alcohol Consumption	Yes	2 (3.0%)	1 (2.9%)	1 (3.0%)	0.983*
	No	65 (97.0%)	33 (97.1%)	32 (97.0%)	
pharmaceutical therapy	Yes	31 (47.0%)	14 (42.4%)	17 (51.5%)	0.459*
	No	35 (53.0%)	19 (57.6%)	16 (48.5%)	

† Based on t-test.

* Based on Chi-Square test.

Table 2. Dietary intake of study participants throughout the study

		Intervention (n=34)	Control (n=33)	95% CI		P value†
		Mean ± SD	Mean ± SD	Lower	Upper	
Energy intake (kcal/day)	Pre	2396.08 ± 462.68	2361.93 ± 534.52	-205.97	274.25	0.777
	Post	2226.16 ± 443.30	2207.60 ± 383.78	-178.73	215.84	0.852
	Change	-169.91 ± 398.79	-154.33 ± 516.96	-238.30	207.13	.0889
Carbohydrate intake (gr/day)	Pre	360.75 ± 78.07	339.00 ± 78.67	-15.71	59.21	0.251
	Post	348.40 ± 87.89	328.02 ± 88.91	-21.88	62.65	0.339
	Change	-12.34 ± 62.76	-10.97 ± 75.80	-34.84	32.11	.0935
Protein intake (gr/day)	Pre	92.27 ± 21.50	82.75 ± 28.14	-2.56	21.60	0.120
	Post	95.34 ± 24.56	85.94 ± 25.30	-2.52	22.33	0.114
	Change	3.07 ± 14.14	3.18 ± 15.93	-7.34	7.11	.0975
Fat intake (gr/day)	Pre	64.31 ± 12.52	66.01 ± 17.65	-9.10	5.70	0.647
	Post	61.51 ± 16.54	65.25 ± 22.40	-13.25	5.77	0.434
	Change	-2.79 ± 13.18	-0.75 ± 19.93	-10.34	6.26	.0625
Fiber intake (gr/day)	Pre	11.94 ± 5.89	10.64 ± 4.34	-2.97	1.60	0.551
	Post	.1541 ± 6.36	.1345 ± .562	-0.09	4.23	0.062
	Change	3.47 ± 7.02	2.80 ± 7.34	-0.12	6.45	.0703
Vitamin D (mcg/day)	Pre	0.92 ± 1.23	1.14 ± 1.38	-1.17	3.77	0.299
	Post	1.40 ± 1.16	.98 ± 0.94	-0.91	4.84	0.179
	Change	0.48 ± 1.46	-.16 ± 1.38	-2.79	4.12	.0703
Vitamin A(mcg/day)	Pre	637.62 ± 304.40	634.04 ± 392.77	-175.14	182.30	0.968
	Post	610.46 ± 210.21	538.28 ± 240.15	-41.44	185.80	0.209
	Change	-22.44 ± 232.21	-95.76 ± 372.56	-85.79	232.43	.0359
Vitamin E (mg/day)	Pre	11.34 ± 7.06	11.62 ± 9.06	-4.19	3.64	0.887
	Post	10.82 ± .583	9.61 ± 5.33	-1.45	3.87	0.368
	Change	-0.51 ± 6.21	-2.00 ± 8.10	-1.99	4.97	.0396
Vitamin C (mg/day)	Pre	108.55 ± 51.69	94.86 ± 59.16	-12.97	40.37	0.309
	Post	94.29 ± 57.16	90.97 ± 44.30	-20.94	27.59	0.785
	Change	-14.26 ± 41.35	-3.88 ± 55.49	-34.01	13.26	.0383
Zinc (mg/day)	Pre	8.75 ± 2.50	8.03 ± 2.96	-1.39	1.23	0.905
	Post	.869 ± .297	8.64 ± 3.56	-1.53	1.62	0.956
	Change	-0.06 ± 2.76	-1.52 ± 2.61	-1.43	1.68	.0875
Selenium (mg/day)	Pre	0.13 ± 0.03	0.15 ± 0.06	-0.04	0.01	0.142
	Post	0.12 ± 0.05	0.13 ± 0.05	-0.04	0.02	0.486
	Change	-0.01 ± 0.05	-0.02 ± 0.06	-0.02	0.03	.0526

† Based on independent t-test.

*statistically significant

Table 3. Comparison of anthropometric measurements and blood lipid parameters between the two Groups

		Intervention (n=34)	Control (n=33)	95% CI		P value†	Adjusted P value§
		Mean ± SD	Mean ± SD	Lower	Upper		
FPG (mg/dL)	Pre	105.26 ± 13.15	101.84 ± 9.31	-2.14	8.97	0.224	
	Post	100.17 ± 13.91	101.11 ± 11.63	-7.19	5.31	0.756	
	Change	-5.09 ± 7.29	-0.98 ± 9.11	-8.35	-0.35	0.033*	0.048*
FI (micro IU/ml)	Pre	13.51 ± 7.47	12.57 ± 10.18	-3.38	5.27	0.665	
	Post	12.16 ± 7.43	13.02 ± 10.05	-5.17	3.45	0.691	
	Change	-1.35 ± 4.90	0.63 ± 4.77	-4.22	0.49	0.120	0.169
HOMA-IR	Pre	3.50 ± 1.92	2.99 ± .257	-0.60	1.63	0.360	
	Post	3.03 ± 1.87	3.15 ± 2.60	-1.24	0.99	0.826	
	Change	-0.47 ± 1.22	0.16 ± 1.17	-1.23	-0.05	0.034*	0.052
QUICKI	Pre	0.32 ± 0.03	0.34 ± 0.05	-0.04	0.01	0.082	
	Post	0.33 ± 0.04	0.33 ± 0.04	0.01	0.02	0.895	
	Change	0.02 ± 0.04	-0.01 ± 0.04	0.01	0.01	0.042*	0.106
FSH (ng/ml)	Pre	4.82 ± 2.55	5.59 ± 1.97	-1.85	0.33	0.178	
	Post	5.06 ± 3.02	.572 ± 2.73	-2.06	0.74	0.351	
	Change	0.24 ± 1.85	0.13 ± 3.15	-1.14	1.34	0.872	0.947
LH (micro IU/ml)	Pre	8.73 ± 5.69	8.27 ± 5.62	-2.35	3.26	0.747	
	Post	8.24 ± 5.34	11.13 ± 11.83	-7.40	1.63	0.205	
	Change	-0.48 ± 5.17	2.85 ± 9.98	-7.25	0.57	0.093	0.171
DHEA (micro gr/dl)	Pre	152.70 ± 107.01	136.74 ± 80.68	-28.86	60.77	0.479	
	Post	138.57 ± 96.92	149.14 ± 78.75	-52.49	31.35	0.616	
	Change	-14.13 ± 32.91	12.4 ± 56.22	-47.99	-4.34	0.020*	0.035*
Estradiol (pg/ml)	Pre	87.92 ± 18.39	88.76 ± 28.71	-12.51	10.82	0.885	
	Post	.9207 ± 14.98	88.70 ± 25.22	-6.87	13.62	0.512	
	Change	4.09 ± 11.45	-0.29 ± 11.79	-1.32	10.11	0.130	0.082
mFg	Pre	9.45 ± 2.88	.1041 ± .540	-2.89	0.98	0.328	
	Post	8.71 ± 2.96	10.54 ± 5.19	-3.90	0.24	0.082	
	Change	-0.91 ± 2.31	0.12 ± 3.50	-2.48	0.42	0.159	0.097
BMI (kg/m^2)	Pre	28.73 ± 4.92	27.28 ± 4.82	-1.98	2.32	0.880	
	Post	27.71 ± 5.01	26.93 ± 4.03	-1.58	3.14	0.513	
	Change	-1.02 ± 4.96	-0.35 ± 4.47	-0.76	0.29	0.375	0.186
WC (cm)	Pre	90.19 ± 12.08	92.04 ± 11.59	-6.99	3.29	0.476	
	Post	88.92 ± 11.78	90.76 ± 11.74	-6.94	3.26	0.482	
	Change	-1.26 ± 3.72	-1.27 ± 2.96	-1.44	1.46	0.988	0.548

† Based on independent t-test.

§ Based on Linear regression (the included variables were: basic value of dependent variable, treatment type, Age and BMI)

*statistically significant

FPG: fasting blood sugar, FI: fasting insulin, HOMA-IR: homeostatic model assessment of insulin resistance, QUICKI: Quantitative insulin sensitivity check index, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, DHEA: Dehydroepiandrosterone, mFg: modified Ferriman–Gallwey (mFG) score, BMI: body mass index, WC: waist circumference.

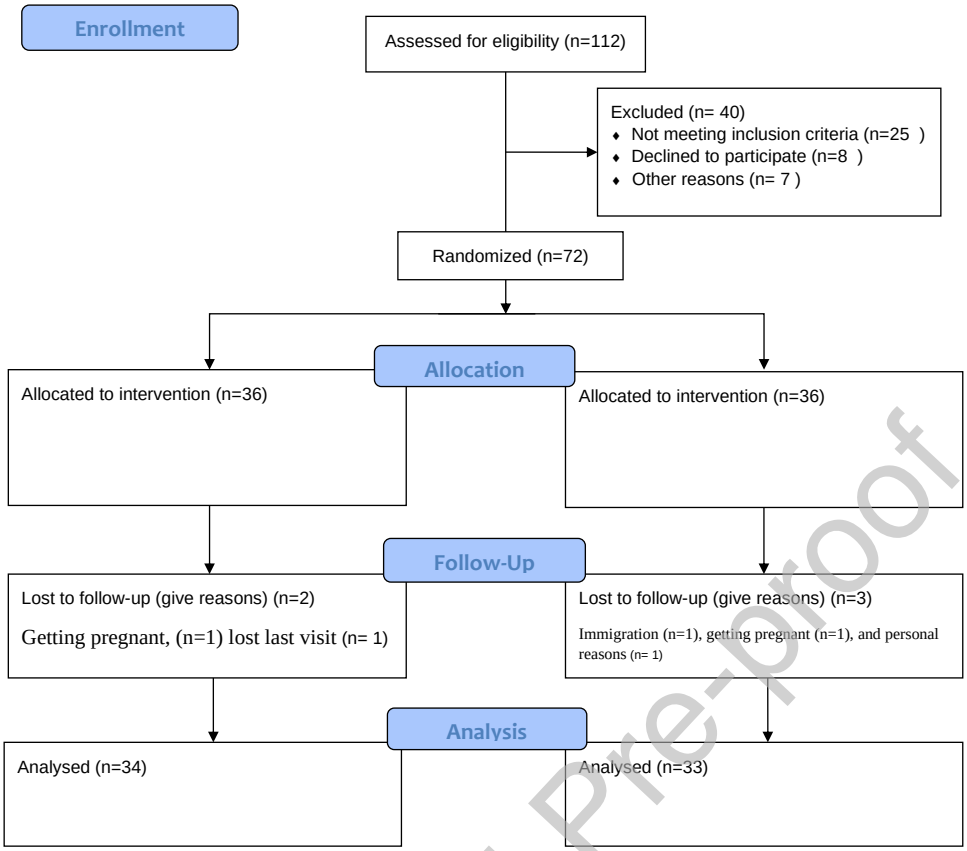
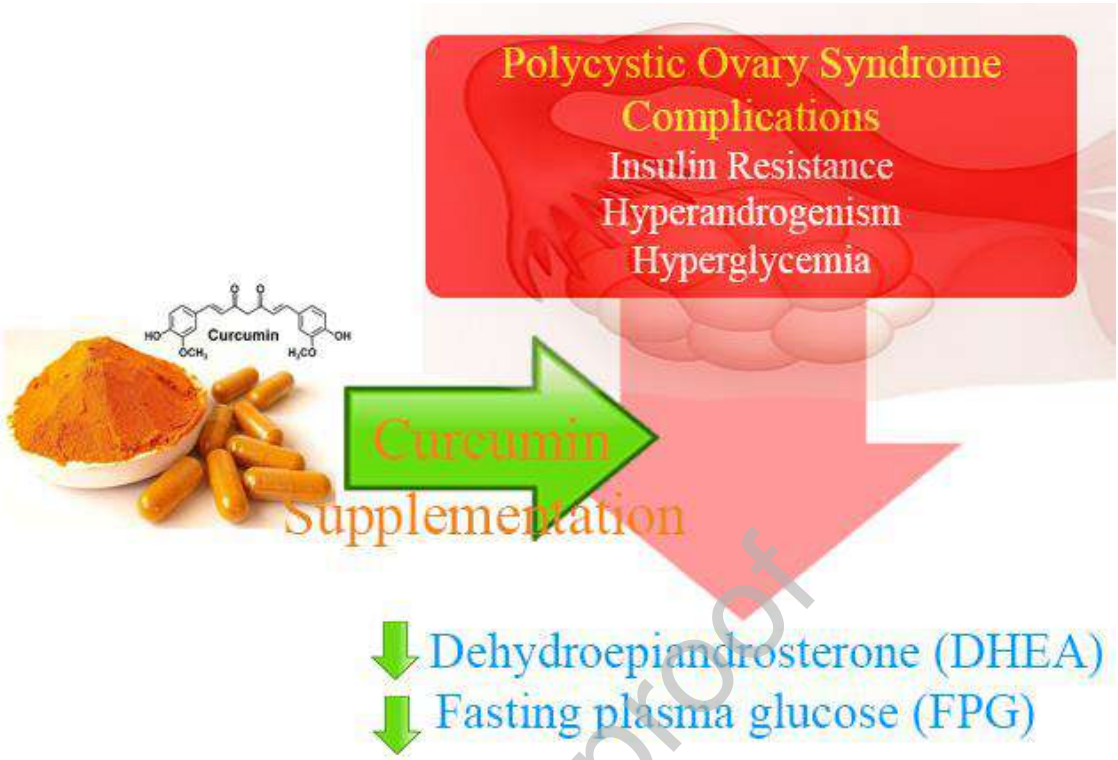


Figure 1. Flow diagram of the study



Graphical Abstract